

Hypoglycemic Unawareness

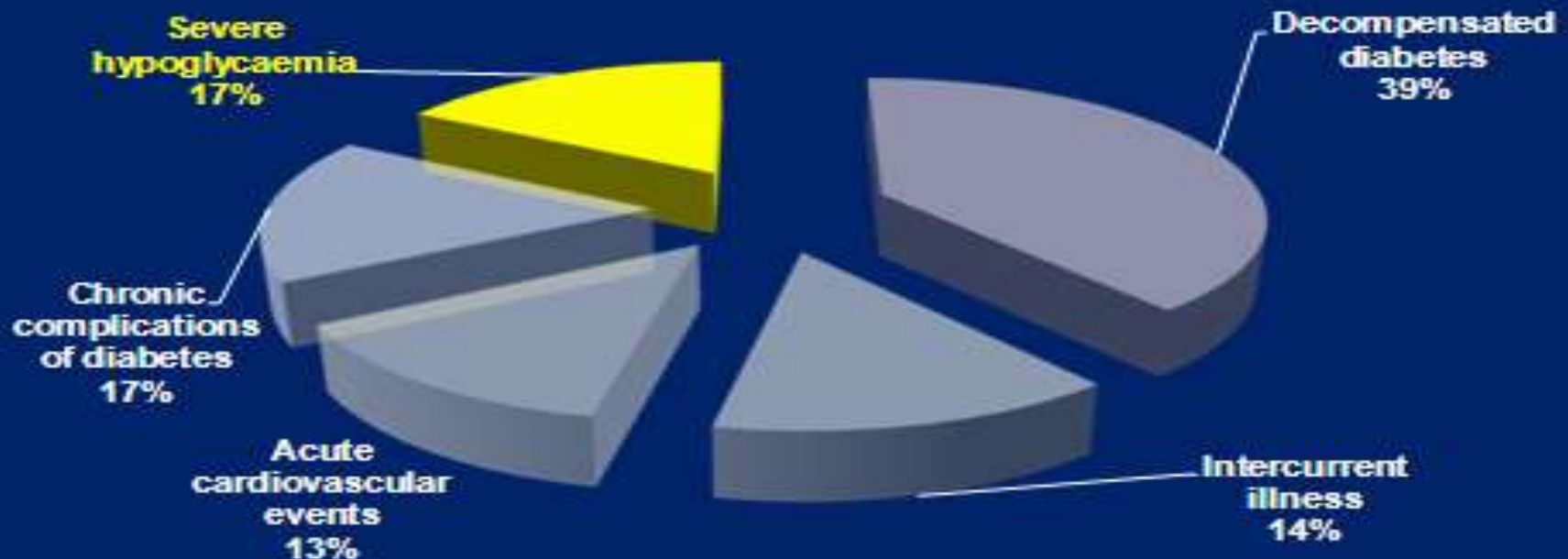
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Severe hypoglycaemia accounts for almost 20% of all hospitalisations for T2DM



T2DM=type 2 diabetes mellitus.
Greco D, et al. *Exp Clin Endocrinol Diabetes*. 2010; 118: 215-219.

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Causes and risk factors

- Antidiabetic treatment
- Delayed or missed meals
- Exercise
- Excessive alcohol consumption
- Age-related impairment of the counter-regulatory hormone responses
- Change in weight
- Renal or liver dysfunction
- Concomitant medications
- Depression



Iatrogenic hypoglycemia

- Iatrogenic hypoglycemia is the limiting factor in the glycemic management of both T1DM & T2DM.



© Can Stock Photo

- Were it not for the potentially devastating effect of hypoglycemia on the brain, diabetes would be rather easy to treat.



Drugs (antidiabetic and others) that are or are not associated with a risk of hypoglycemia.

Associated with a risk of hypoglycemia

| | |
|-------------|---|
| OADs | Sulfonylureas, meglitinides (nateglinide, repaglinide), glimepiride |
| Insulin | All insulins |
| Other drugs | Alcohol, aspirin, warfarin, allopurinol or probenecid when in combination with antidiabetic medications |

Not usually associated with a risk of hypoglycemia on their own

| | |
|------|--|
| OADs | Alpha-glucosidase inhibitors, biguanides (metformin), thiazolidinediones, GLP-1 agonists, DPP-4 inhibitors, SGLT2 inhibitors |
|------|--|



Frequency

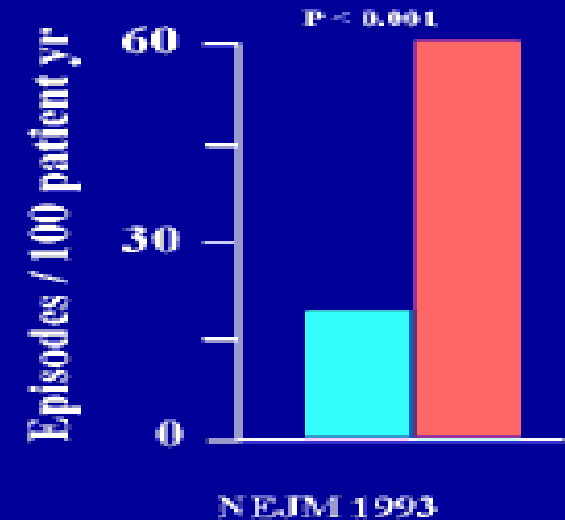
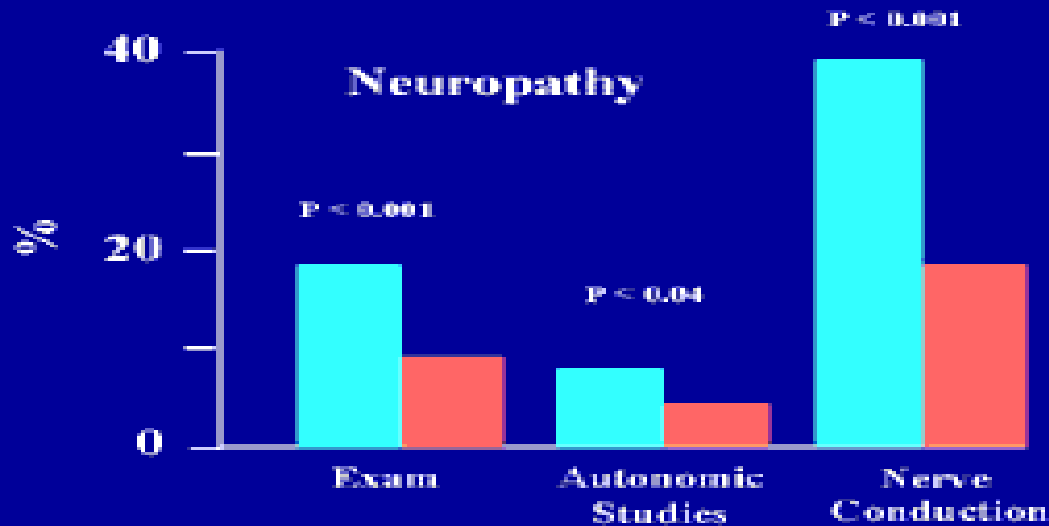
- Hypoglycemia is a fact of life in type 1 DM.
- Hypoglycemic rates are **15**-fold lower in orally treated and approximately **6**-fold lower in insulin-treated patients with type 2 DM than in patients with type 1 DM.
- The frequency of severe hypoglycemia increases over time in patients with type 2 diabetes



DCCT Study

Intensive Rx
Conventional Rx

Severe Hypoglycemia



- A total of 65% of patients in the intensive group vs. 35% of patients in the conventional group had at least one episode of severe hypoglycemia by the study end.
- The overall rates of severe hypoglycemia were 61.2 per 100 patient-years vs. 18.7 per 100 patient-years in the intensive and conventional treatment groups, respectively.

(DCCT 1994; 1997)

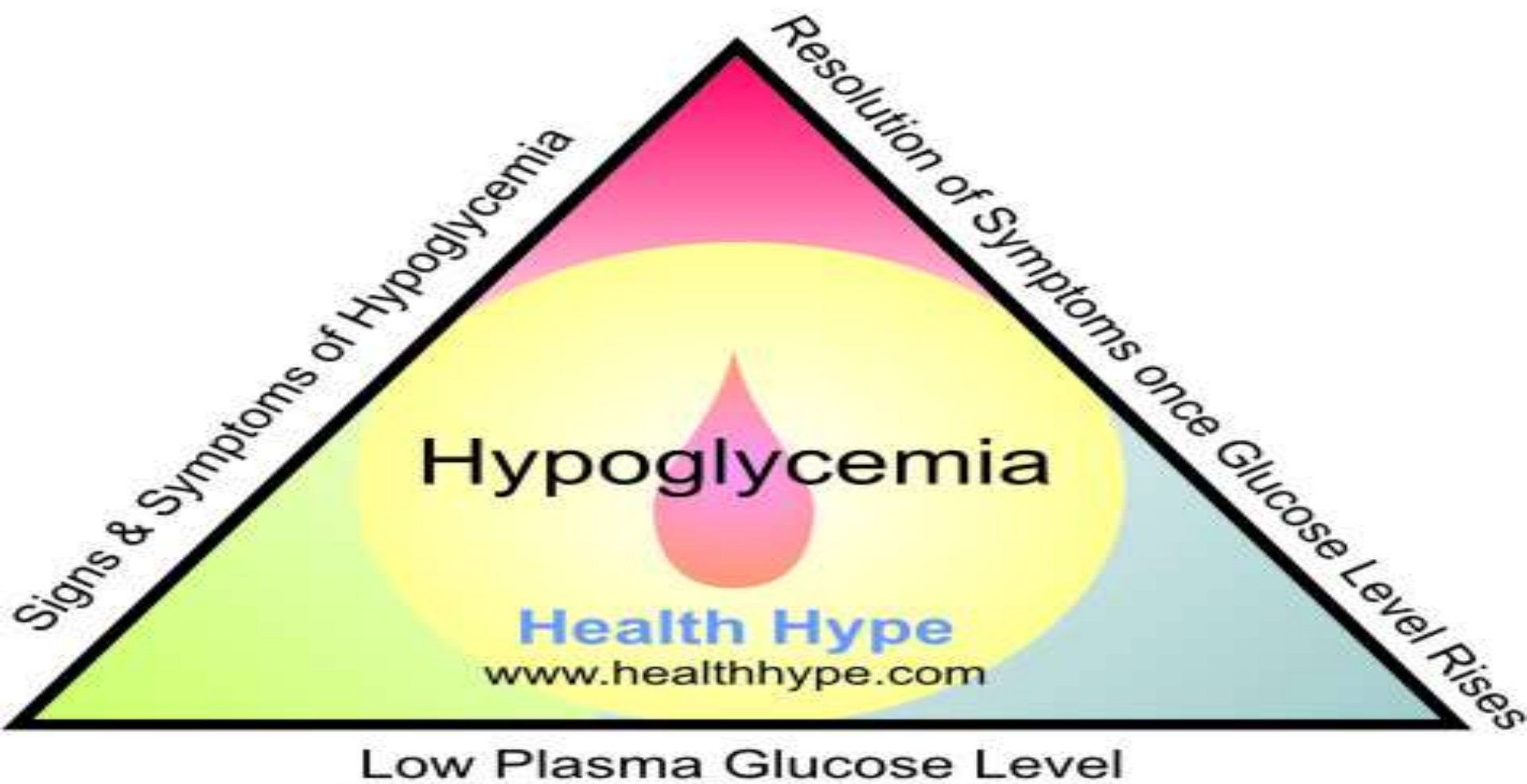


Symptoms

| Classification | Typical symptoms |
|-----------------|--|
| Neurogenic | Palpitation, anxiety, sweating, hunger |
| Neuroglycopenic | Cognitive impairment, confusion, behavioral changes |
| | Seizures, Loss of consciousness (even death) in severe cases |



Whipple's Triad



Biochemical definition of hypoglycemia

❖ The exact biochemical definition of hypoglycemia varies between associations, with glycemic thresholds defined as follows:

- European Medicines Agency (EMA), 3.9 mmol/L (70 mg/dL) .
- American Diabetes Association (ADA), 3.9 mmol/L (70 mg/dL) .
- Canadian Diabetes Association (CDA), 4.0 mmol/L (72 mg/dL) .





ADA/Endocrine Society: Classification of Hypoglycemia in Diabetes

Alert value for hypoglycemia:
PG ≤ 70 mg/dL (≤ 3.9 mmol/L)

| | |
|--|--|
| Severe hypoglycemia | <ul style="list-style-type: none"> Requires assistance of another person to administer carbohydrates, glucagon, or take other actions PG concentrations may not be available during an event <ul style="list-style-type: none"> Neurological recovery following euglycemia considered sufficient evidence that event was induced by low PG |
| Documented symptomatic hypoglycemia | <ul style="list-style-type: none"> Typical hypoglycemia symptoms are accompanied by measured PG ≤ 70 mg/dL (≤ 3.9 mmol/L) |
| Asymptomatic hypoglycemia | <ul style="list-style-type: none"> Not accompanied by typical hypoglycemia symptoms but with measured PG ≤ 70 mg/dL (≤ 3.9 mmol/L) |
| Probable symptomatic hypoglycemia | <ul style="list-style-type: none"> Typical hypoglycemia symptoms not accompanied by PG determination but likely caused by PG ≤ 70 mg/dL (≤ 3.9 mmol/L) |
| Pseudo-hypoglycemia | <ul style="list-style-type: none"> Reports of typical hypoglycemia symptoms with measured PG > 70 mg/dL (> 3.9 mmol/L) but approaching hypoglycemia threshold |

PG=plasma glucose

Seaquist ER, Anderson J, Childs B, et al. 2013. *Diabetes Care*. Epub ahead of print.



Response to hypoglycemia

The initial response is the cessation of insulin secretion at a blood glucose threshold of ~ 4.6 mmol/L (~ 83 mg/dL).

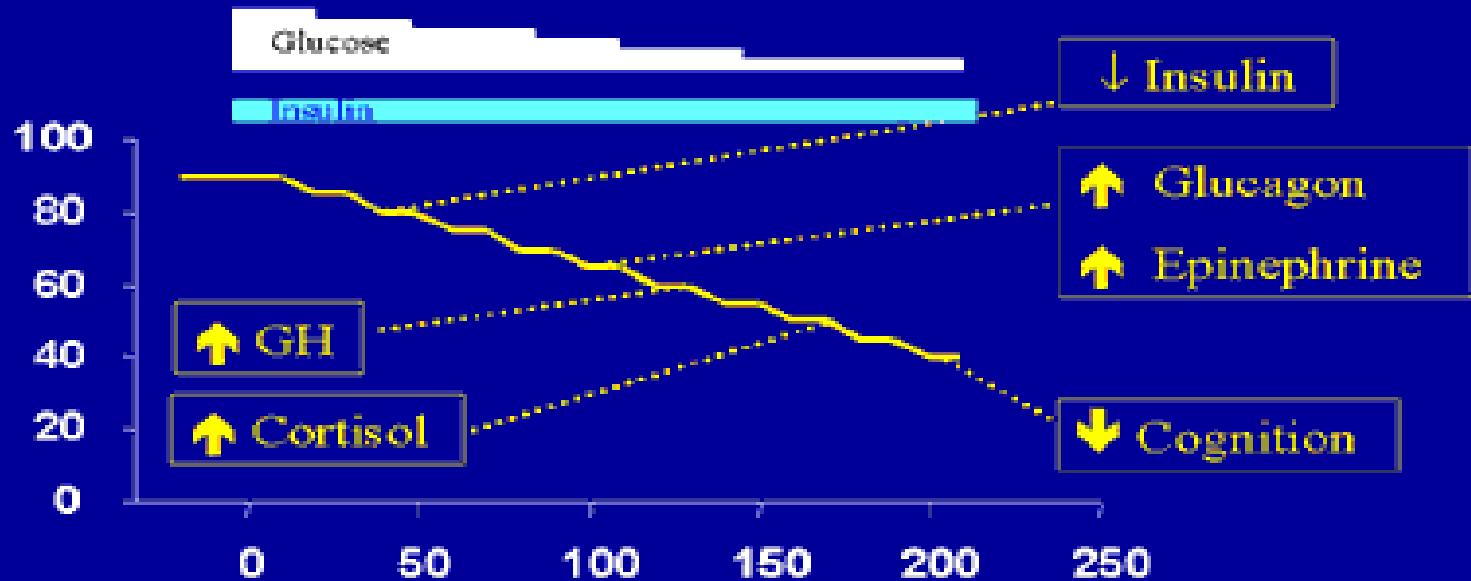
This is followed by counter-regulatory hormone responses (starting at 3.8 mmol/L (68.4 mg/dL)), primarily the release of the fast-acting glucagon and epinephrine (adrenaline) hormones



EEG, electroencephalogram



Insulin Counter Regulatory Response in Adults



Bohl, Gerich, Cryer



Response to hypoglycemia

- In people with type 1 diabetes
 - An absolute insulin deficiency precludes the first-line defense against falling blood glucose levels.
 - In addition, with the loss of the pancreatic α -cell glucagon secretory response, the last remaining defenses are the release of epinephrine and autonomic warning symptoms.

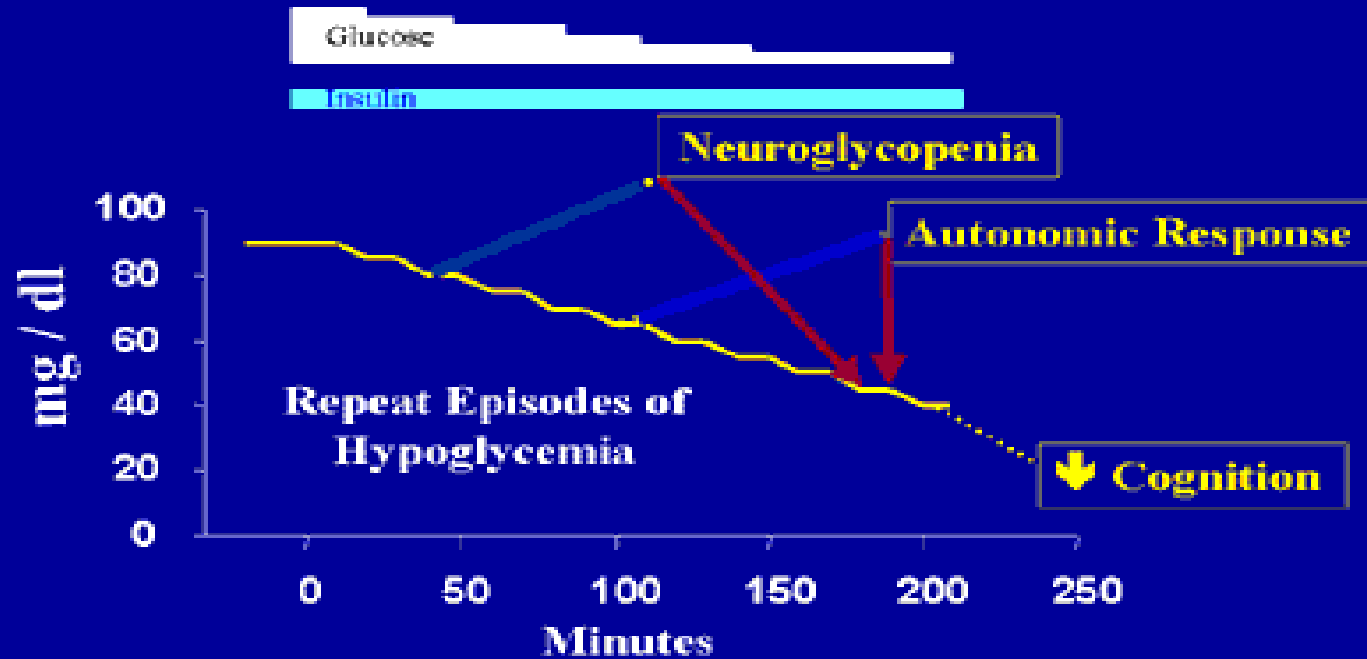


Response to hypoglycemia

- In people with type 2 diabetes
 - The residual β -cell function initially preserves the insulin first-line defense.
 - However, with the progressive loss of β -cell function and repeated hypoglycemic events, the endogenous glucose counter-regulatory response is lost .



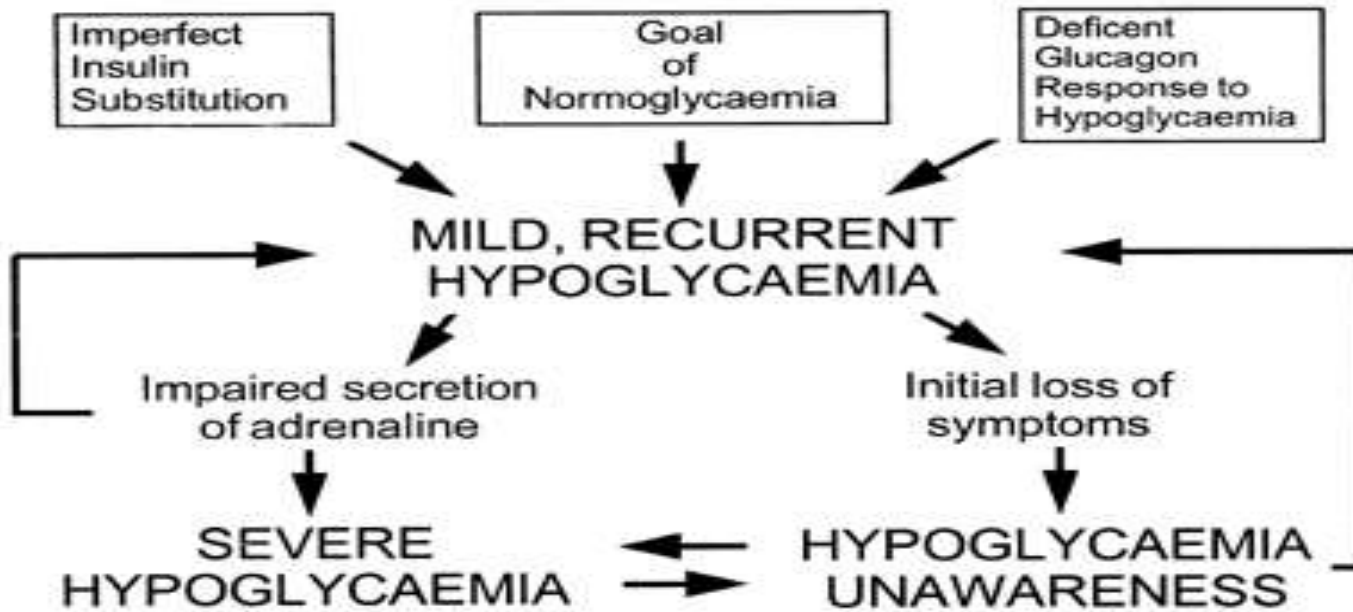
Hypoglycemic Unawareness With Recurrent Hypoglycemic Episodes



With repeated episodes, threshold shift, such that neuroglycopenic & autonomic responses get down very close to the cognitive response failure



INTENSIVE INSULIN THERAPY OF IDDM



Vicious circle where recurrent hypoglycemia during intensive treatment of type 1 DM causes hypoglycemia unawareness and impaired counterregulation, ultimately increasing the risk for severe hypoglycemia.



Hypoglycemia-associated Autonomic Failure (HAAF)

1. Defective glucose counterregulation
2. Hypoglycemia unawareness



Hypoglycemia unawareness

Definition

Onset of hypoglycemia before the appearance of autonomic warning symptoms.

“ patient inability to perceive hypoglycemic symptoms “



History

- In 1987, a preliminary report contended that hypoglycemic unawareness became more prevalent in diabetics transferred from beef-pork to human insulin.



Frequency

Type 1 DM > type 2 DM

- 25% of patients with type 1 DM had “partial” or “absent” awareness .
- Among *insulin-treated patients with type 2 DM*, 9.8% had trouble correctly identifying hypoglycemic events .



- Hypoglycemic unawareness is associated with a **25** fold greater frequency of severe hypoglycemia



When to suspect hypoglycemia unawareness

- A self-reported history of impaired or absent perception of autonomic symptoms during hypoglycemia.
- Frequent episodes of recurrent hypoglycemia occur within hours to days
- More than one episode of severe hypoglycemia that required the assistance of another over the preceding year.
- Family report of more frequent episodes of hypoglycemia.



- Hypoglycemia unawareness while awake
- Sleeping patient (nocturnal hypoglycemic awareness)



Nocturnal hypoglycemia

- Nocturnal hypoglycemia is common, especially in patients with **T1DM**.
- During the DCCT Trial:
 - 43% of all hypoglycemic episodes and 55% of severe episodes reported occurred during sleep.
 - **> 49% of episodes occur without symptoms.**



CGM Data

- A recent analysis of 36,467 nights in 176 young subjects with T1DM revealed that hypoglycemic events (2 consecutive CGM readings ≤ 60 mg/dL in 20 minutes) occurred during **8.5%** of nights.
- The duration of hypoglycemia was ≥ 2 hours on **23%** of hypoglycemic nights.

JDRF CGM Randomized Clinical Trial ,Diabetes Care. 2010



Clinical features of nocturnal hypoglycemia

- vivid dreams or nightmares
- night sweats
- poor sleep quality or restlessness during sleep
- morning headache, fatigue, mood changes
- enuresis in children.
- Coma, seizures, serious injuries such as fractures, joint dislocations, cardiac arrhythmia, or sudden death **“dead-in-bed syndrome”**.



Gertzman J et al., Diabetes.2005;52(suppl 1):A146.



Diagnosis



Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society

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OBJECTIVE—To review the evidence about the impact of hypoglycemia on patients with diabetes that has become available since the past reviews of this subject by the American Diabetes Association and The Endocrine Society and to provide guidance about how this new information should be incorporated into clinical practice.

PARTICIPANTS—Five members of the American Diabetes Association and five members of The Endocrine Society with expertise in different aspects of hypoglycemia were invited by the Chair, who is a member of both, to participate in a planning conference call and a 2-day meeting that was also attended by staff from both organizations. Subsequent communications took place via e-mail and phone calls. The writing group consisted of those invitees who participated in the writing of the manuscript. The workgroup meeting was supported by educational grants to the American Diabetes Association from Lilly USA, LLC and Novo Nordisk and sponsorship to the American Diabetes Association from Sanofi. The sponsors had no input into the development of or content of the report.

EVIDENCE—The writing group considered data from recent clinical trials and other studies to update the prior workgroup report. Unpublished data were not used. Expert opinion was used to develop some conclusions.

CONSENSUS PROCESS—Consensus was achieved by group discussion during conference calls and face-to-face meetings, as well as by iterative revisions of the written document. The document was reviewed and approved by the American Diabetes Association's Professional Practice Committee in October 2012 and approved by the Executive Committee of the Board of Directors in November 2012 and was reviewed and approved by The Endocrine Society's Clinical Affairs Core Committee in October 2012 and by Council in November 2012.

CONCLUSIONS—The workgroup reconfirmed the previous definitions of hypoglycemia in diabetes, reviewed the implications of hypoglycemia on both short- and long-term outcomes, considered the implications of hypoglycemia on treatment outcomes, presented strategies to prevent hypoglycemia, and identified knowledge gaps that should be addressed by future research.

In 2005, the American Diabetes Association Workgroup on Hypoglycemia released a report entitled "Defining and Reporting Hypoglycemia in Diabetes" (1). In that report, recommendations were primarily made to advise the U.S. Food and Drug Administration (FDA) on how hypoglycemia should be used as an end point in studies of new treatments for diabetes. In 2009, The Endocrine Society released a clinical practice guideline entitled "Evaluation and Management of Adult Hypoglycemic Disorders," which summarized how clinicians should manage hypoglycemia in patients with diabetes (2). Since then, new evidence has become available that links hypoglycemia with adverse outcomes in older patients with type 2 diabetes (3–6) and in children with type 1 diabetes (7,8). To provide guidance about how this new information should be incorporated into clinical practice, the American Diabetes Association and The Endocrine Society assembled a new Workgroup on Hypoglycemia in April 2012 to address the following questions:

1. How should hypoglycemia in diabetes be defined and reported?
2. What are the implications of hypoglycemia on both short- and long-term



Table 2—Hypoglycemia Patient Questionnaire

Name _____

First _____ Middle _____ Last _____

Today's date _____

1. To what extent can you tell by your symptoms that your blood glucose is LOW?

____ Never ____ Rarely ____ Sometimes ____ Often ____ Always

2. In a typical week, how many times will your blood glucose go below 70 mg/dL?

____ a week

3. When your blood glucose goes below 70 mg/dL, what is the usual reason for this?

4. How many times have you had a severe hypoglycemic episode (where you needed someone's help and were unable to treat yourself)?

Since the last visit ____ times

In the last year ____ times

5. How many times have you had a moderate hypoglycemic episode (where you could not think clearly, properly control your body, had to stop what you were doing, but you were still able to treat yourself)?

Since the last visit ____ times

In the last year ____ times

6. How often do you carry a snack or glucose tablets (or gel) with you to treat low blood glucose?

Check one of the following:

Never ____ Rarely ____ Sometimes ____ Often ____ Almost always ____

7. How LOW does your blood glucose need to go before you think you should treat it?

Less than ____ mg/dL.

8. What and how much food or drink do you usually treat low blood glucose with?

9. Do you check your blood glucose before driving? Check one of the following:

Yes, always ____ Yes, sometimes ____ No ____

10. How LOW does your blood glucose need to go before you think you should not drive?

____ mg/dL.

11. How many times have you had your blood glucose below 70 mg/dL while driving?

Since the last visit ____ times

In the last year ____ times

12. If you take insulin, do you have a glucagon emergency kit?

Yes ____ / No ____

13. Does a spouse, relative, or other person close to you know how to administer glucagon?

Yes ____ / No ____

Seaquist E. R. et al. Diabetes Care 2013;36:1384-1395



Table 3—Hypoglycemia Provider Checklist

Name _____
First Middle Last
Today's date _____

1. __ Reviewed the Hypoglycemia Patient Questionnaire
2. __ Questioned the patient about circumstances surrounding severe or moderate hypoglycemia
3. __ Discussed strategies to avoid hypoglycemia with the patient
4. __ Made medication changes where clinically appropriate
5. __ Recommended carrying snack and/or glucose tablets where appropriate and provided instructions for how to use them (take 15 g glucose, wait 15 min, and remeasure blood glucose; repeat if hypoglycemia persists). A 1-page patient handout on treating hypoglycemia is available at <http://clinical.diabetesjournals.org/content/30/1/38>
6. __ Prescribed glucagon if appropriate



Methods of assessing awareness of hypoglycemia

- The Gold method poses the question “**do you know when your hypos are commencing?**” The respondent then completes a 7-point Likert scale, with 1 representing “always aware” and 7 representing “never aware”. A score of ≥ 4 implies impaired awareness of hypoglycemia.

Gold AE et al., *Diabetes Care* 17:697–703, 1994



Methods of assessing awareness of hypoglycemia

- The Clarke method comprises eight questions characterizing the participant's exposure to episodes of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and symptomatic responses to, hypoglycemia. A score of four or more implies impaired awareness of hypoglycemia.

Clarke WL et al., *Diabetes Care* **18**:517–522, 1995



Methods of assessing awareness of hypoglycemia

- The Pedersen-Bjergaard method requires the patient to respond to the question “can you feel when your blood is low?” requiring the selection of one response from “always” “usually” “sometimes” or “never”.
- Only patients who answer “always” are considered to have normal symptomatic awareness of hypoglycemia; the others are designated as having impaired or absent awareness.

Pedersen-Bjergaard U et al., *Lancet* **357**:1248–1253,2001



Methods of assessing awareness of hypoglycemia

- The three methods currently available to assess symptomatic awareness of hypoglycemia were evaluated for their concordance in identifying impaired awareness of hypoglycemia.
- In conclusion, for clinical and research use, the Clarke and Gold methods should be used preferentially, either separately or in combination, to identify people with type 1 diabetes who have impaired awareness of hypoglycemia.

Geddes J et al., Diabetes care (2007)



Management



2–3 weeks of avoidance of iatrogenic hypoglycemia reverses hypoglycemia unawareness.



Practical treatment strategies for patients with hypoglycemia unawareness

Blood glucose monitoring (SMBG)

Frequent blood glucose monitoring, especially before meals, at bedtime and during suggestive symptoms

blood glucose monitoring between 2^{AM} & 5^{AM} at least 3 times weekly

Evaluate blood glucose targets & avoid low blood glucose values



Practical treatment strategies for patients with hypoglycemia unawareness

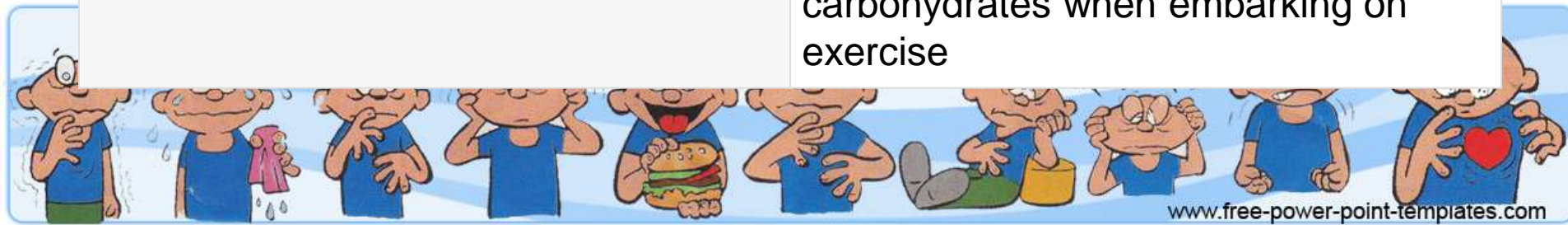
Diet & Exercise

Ensure adequate caloric intake with interprandial and bedtime snacks, as required, strictly based on blood glucose measurements

Ensure blood glucose measurements are taken before, during and after exercise

Pre-exercise – additional caloric intake if blood glucose values indicate falling glucose levels

Ensure access to readily absorbable carbohydrates when embarking on exercise



Practical treatment strategies for patients with hypoglycemia unawareness

Insulin

Adjust insulin regimen to achieve and maintain target glucose levels

Consider using basal insulin analogs to decrease the risk of nocturnal hypoglycemia

Consider using carefully adjusted, rapid-acting insulin analogs to decrease the risk of interprandial hypoglycemia

Consider a CSII pump or CGM device as appropriate





ADA/Endocrine Society: Impact of Hypoglycemia on Glycemic Targets

Individualize glycemic targets based on:
age • life expectancy • comorbidities • preferences •
assessment of hypoglycemia impact on patient's life

Patient-Centered Goals

Healthy adults
with diabetes

Lowest A1C that does not cause severe hypoglycemia, preserves hypoglycemia awareness, and results in acceptable number of documented episodes of symptomatic hypoglycemia

Type 1
diabetes

Achieve glucose levels low enough to prevent hypoglycemia symptoms; strategies that avoid hypoglycemia may not be possible. Relax goals with advanced complications, limited life expectancy, long-standing disease

Type 2
diabetes

Risk related to types of medications used. A1C <7.0% may be appropriate for recent-onset type 2 diabetes; less aggressive goals as disease progresses, or with known CVD, extensive comorbidities, limited life expectancy

Seaquist ER, Anderson J, Childs B, et al. 2013. *Diabetes Care*. Epub ahead of print.

Seaquist E. R. et al. *Diabetes Care* 2013;36:1384-1395



Summary



- Hypoglycemia represents a significant barrier to improve diabetes care.
- Healthcare providers need to be aware of under-recognized hypoglycemic events to ensure the best possible outcome for their patients.
- Improving patient education, modifying treatment, and incorporating the latest technological advances may all help to reduce the frequency of hypoglycemic episodes, minimize the progression toward impaired awareness, and improve overall patient care.



THANK
You

